

AMENDMENTS TO THE SPECIFICATION

Please substitute the following replacement paragraph(s) for the previously-pending versions of such paragraph(s). The replacement paragraph(s) are marked-up to show changes from the previously-pending versions thereof. Please add the following new paragraph(s) as indicated.

**\*\* Replace paragraph [0001] with the following replacement paragraph:**

**[0001]** The present invention is related to, and claims priority to co-owned, co-pending U.S. patent application Ser. No. 60/187,566 entitled "Apparatus and Methods for Multi-Variable Optimization of Reaction Systems and Other Chemical Processing Microsystems", filed March 7, 2000 by Bergh *et al.*, and to co-owned, co-pending U.S. patent application Ser. No. 60/229,984 entitled "Apparatus and Methods for Optimization of Process Variables in Reaction Systems and Other Chemical Processing Systems", filed September 2, 2000 ~~2001~~ by Bergh *et al.*

**\*\* Replace paragraph [0038] with the following replacement paragraph:**

**[0038]** The present invention is related to the following patents and/or patent applications, each of which is hereby incorporated by reference for all purposes, including for the purpose of combination of various features disclosed in the various related applications to various features disclosed herein, to the highest extent practical, based on the knowledge in the art, and coupled with the guidance of this application and the related applications: (1) co-owned, co-pending U.S. patent application Ser. No. 60/187,566 entitled "Apparatus and Methods for Multi-Variable Optimization of Reaction Systems and Other Chemical Processing Microsystems", filed March 7, 2000 by Bergh *et al.*, (2) co-owned, co-pending U.S. patent application Ser. No. 60/229,984 entitled "Apparatus and Methods for Optimization of Process Variables in Reaction Systems and Other Chemical Processing Systems", filed September 2, 2000~~2001~~ by Bergh *et al.*; (3) co-owned, co-pending U.S. patent application Ser. No. 09/093,870, entitled "Parallel Fixed-Bed Reactor and Fluid Contacting Apparatus and Method", filed June 9, 1998 by Guan *et al.*, and now issued as U.S. Patent No. 6,149,882; (4) to co-owned, co-pending U.S. patent application Ser. No. 09/518,794, entitled "Chemical Processing Microsystems, Diffusion-Mixed Microreactors and Methods for Preparing and Using Same", filed March 3, 2000 by Bergh *et al.* now issued as U.S. Patent No. 6,749,814; (5) U.S. Serial No. 60/274,065, entitled "Parallel Flow

Reactor Having Improved Thermal Control” filed on the date even herewith (March 7, 2001) by Bergh *et al.* now perfected as U.S. Serial No. 10/094,257 filed March 7, 2002 by Bergh *et al.*; (6) U.S. Serial No. 60/274,022, entitled “Gas Chromatograph Injection Valve Having Microvalve Array” filed on the date even herewith (March 7, 2001) by Bergh *et al.* now perfected as U.S. Serial No. 10/092,364 filed March 6, 2002 by Bergh *et al.*, and as U.S. Serial No. 10/092,035 filed March 6, 2002 by Bergh *et al.*, now issued as U.S. Patent No. 6,742,544; and (7) U.S. Serial No. 09/801,430, entitled “Parallel Gas Chromatograph With Microdetector Array” filed on the date even herewith (March 7, 2001) by Srinivasan *et al.* now issued as U.S. Patent No. 6,701,774. Further reference to several of these applications is made below, in the context of the present invention.

**\*\* Replace paragraph [0049] with the following replacement paragraph:**

**[0049]** In general, the particular nature, type, design and/or configuration of the flow restrictor is not narrowly critical. The inlet flow restrictors, outlet flow restrictors and/or feed-composition flow restrictors are a portion of a fluid distribution path that provides a resistance to flow, and typically, provides a greater resistance to flow than the immediately upstream portion of the fluid distribution path of the chemical processing system. For chemical reaction systems, the flow restrictors can provide a resistance to flow between a reactant source and the reactors, or between the reactors and an effluent sink. For a feed distribution system (or subsystem) the flow restrictors can provide a resistance to flow between a feed component source and a mixing zone (*e.g.*, mixing cavity, combined channel, reaction cavity, *etc.*). Preferred flow restrictors include passive flow restrictors such as capillaries, microcapillaries, small channels, channels having orifices, and microfluidic channels (*e.g.*, including microfabricated channels), among others. In preferred embodiments of the invention, discussed in further detail below, the flow restrictors are microfluidic channels, typically formed using microfabrication techniques, and can be integral with a substrate or with one or more microchip bodies mounted – fixedly or detachably – on a substrate. A further description of preferred flow restrictors is provided below, as well as in each of the aforementioned co-pending patent applications of Guan *et al.* (now U.S. Patent No. 6,149,882) and of Bergh *et al.* (U.S. Ser. No. 09/518,794 now U.S. Patent No. 6,749,814). Although flow control is preferably effected with flow restrictors, in some embodiments of the invention, it is contemplated that active flow-control elements can be used to control flow. The

use of such active flow-control elements can be advantageously effected, for example, in reaction system embodiments in which the active flow-control elements are microfabricated or are integral with a substrate or with one or more microbodies mounted on the substrate.

**\*\* Replace paragraph [0119] with the following replacement paragraph:**

**[0119]** Process temperature (*e.g.*, reaction temperature) can be controllably varied in combination with the aforementioned approaches for controlling reactor feed compositions, reactant flow rates and reactor pressure. With further reference to Figure 7A, for example, the chemical processing system 10 can also include a temperature control system (not shown) adapted to provide a temperature gradient or other desired temperature variation across the array 100 of reactors 600. The temperature control can be for a group of reactors or for individual reactors, as desired, and can generally be as described below, and also as described in the Guan *et al.* (U.S. Patent No. 6,149,882) and Bergh *et al.* (U.S. Serial No. 09/518,794 now U.S. Patent No. 6,749,814) applications.

**\*\* Replace paragraph [0120] with the following replacement paragraph:**

**[0120]** Particular approaches for varying temperatures across a library of candidate catalysts can vary depending on the particular type of reactor system employed. Exemplary approaches for varying temperature across a library of different candidate materials are disclosed in connection with the aforementioned co-pending applications of Guan *et al.* (U.S. Patent No. 6,149,882) and of Bergh *et al.* (U.S. Serial No. 09/518,794 now U.S. Patent No. 6,749,814). In one approach, a temperature gradient can be advantageously applied to one or more embodiments of reaction systems (or, other chemical processing systems) where the number of reactors seeing different temperatures is substantially enhanced, by orientating an array of reactors in a slightly skewed manner relative to the orientation of the temperature-contours (lines of constant temperature). The embodiment shown and discussed in connection with Figures 8E is exemplary.

**\*\* Replace paragraph [0121] with the following replacement paragraph:**

**[0121]** Particularly preferred parallel flow reaction systems can include a reactor module that comprises four or more parallel flow reactors having separate and independent temperature control for each of the four or more reactors. Substantial thermal management challenges exist

for such reactor modules in which the four or more flow reactors are close-packed – that is, in which the four or more reactors have a spatial density (taken along one or more cross-sections) of not less than about 1 reactor / 100 cm<sup>2</sup>, preferably not less than about 1 reactor / 50 cm<sup>2</sup>, more preferably not less than about 1 reactor / 10 cm<sup>2</sup>, and, in some applications, not less than about 1 reactor / cm<sup>2</sup>, not less than about 2 reactors / cm<sup>2</sup>, not less than about 1 reactor / mm<sup>2</sup>. A preferred approach for establishing thermal independence between each of the four or more reactors, such that simultaneous independent temperature control can be effected for each of the four or more reactors without substantial thermal interference from adjacent reactors is disclosed in U.S. Serial No. 60/274,065, entitled “Parallel Flow Reactor Having Improved Thermal Control” filed on the date even herewith (March 7, 2001) by Bergh *et al.* now perfected as U.S. Serial No. 10/094,257 filed March 7, 2002 by Bergh *et al.* Briefly, as described therein, independent temperature control for each of the four or more reactors is effected using separately-controlled heating elements (*e.g.* resistive heating elements such as coil heaters) around each of the four or more reactors, while thermal isolation between the four or more reactors is accomplished by fluid-based heat exchange with an external heat sink. In preferred embodiments, the heat flux being applied to each of the reactors has an axial profile (taken along the length of the flow reactor, with the direction of flow) that can be varied (fixedly varied, or controllably varied) to compensate for variations in the heat-flux profile associated with the circulating heat-exchange fluid cooling the reactors, and to compensate for the varied locations of the four or more reactors relative to other reactors and to the external environment (*e.g.* centered reactors versus reactors near an external edge of the reactor module). Hence, design and/or control of the heating elements for each of the reactors can effect a substantially axially-uniform temperature profile for each of the four or more independently. Although especially useful in connection with parallel flow reactors, the temperature-control system disclosed in the ~~aforementioned~~aforementioned patent application can have applications for control of other types of reaction systems (*e.g.*, batch reactors, semi-continuous reactors) and/or in non-reaction chemical processing systems (*e.g.* calcining of heterogeneous catalysts) where parallel, independent temperature control is desirable.

**\*\* Replace paragraph [0126] with the following replacement paragraph:**

**[0126]** A detection system especially preferred for use in connection with the reaction system of the present invention can comprise a multi-channel gas chromatograph as disclosed in co-owned, co-pending U.S. Serial. No. 60/222,540, entitled "Parallel Gas Chromatograph with Microdetector Array" filed August 2, 2000 by Srinivasan *et al.*, as well as in U.S. Serial No. 09/801,430, entitled "Parallel Gas Chromatograph with Microdetector Array" filed on the date even herewith (March 7, 2001) by Srinivasan *et al.* now issued as U.S. Patent No. 6,701,774. Reactor effluents discharged from each of the four or more reactors can be simultaneously ~~simultaneously~~ injected into such a multi-channel (*i.e.* parallel) gas chromatograph using a parallel injection valve, such as is disclosed in U.S. Serial No. 60/274,022, entitled "Gas Chromatograph Injection Valve Having Microvalve Array" filed on the date even herewith (March 7, 2001) by Bergh *et al.* now perfected as U.S. Serial No. 10/092,364 filed March 6, 2002 by Bergh *et al.*, and as U.S. Serial No. 10/092,035 filed March 6, 2002 by Bergh *et al.*, now issued as U.S. Patent No. 6,742,544.

**\*\* Replace paragraph [0131] with the following replacement paragraph:**

**[0131]** The plurality of reactors are two or more reactors, preferably four or more reactors, and more preferably nine or more reactors. Higher numbers of reactors, including sixteen, twenty-four, forty-eight or ninety-six or more reactors are contemplated. When an array of microreactors is used in connection with the invention, the number of reactors can be hundreds or thousands. Additional general features of the reactors together with preferred number of reactors, reactor types, types of candidate materials optionally included within the reactors (especially catalyst candidate materials), variations in composition of the candidate materials (especially variations in catalysts and/or catalyst precursors) loading / unloading of candidate materials into / from the reactors, configurations of arrays of reactors, planar densities of reactors, specific reactor designs, and reactor fabrication approaches are as described in the aforementioned co-pending U.S. patent applications of Guan *et al.* (U.S. Patent No. 6,149,882) and Bergh *et al.* (U.S. Serial No. 09/518,794 now U.S. Patent No. 6,749,814), collectively referred to hereinafter as the "Guan *et al.* and Bergh *et al.* applications." Such additional general features are hereby specifically incorporated by reference.

**\*\* Replace paragraph [0132] with the following replacement paragraph:**

**[0132]** Referring to Figure 8A, an integrated chemical reaction system 10 comprising a flow-through reactor design (*e.g.*, analogous to a plug-flow reactor) can comprise a plurality of microreactors 600 formed in one or more laminae 100. The material-containing laminate 100 comprises a candidate material 920 such as bulk catalyst (*e.g.*, as beads, pellets or particulates, *etc.*) or supported catalysts contained within the microreactors by a porous barrier 126 (*e.g.*, frits, porous plug, *etc.*, as described above). As shown, the plurality of microreactors 600 are sealed and heated by adjacent temperature control blocks – shown as adjacent heaters 980 – with releasable seals 300 (*e.g.*, gaskets, such as metal gaskets with optional knife-edge seal) situated between the heaters 980 and the microreactor laminae 100. Reactants 20 are provided to the microreactors 600 through an inlet distribution manifold 500 in fluid communication with the microreactors 600 via connecting channels 550. The distribution manifold can comprise a first set of inlet flow restrictors (not shown in Figure 8A), and optionally, a feed-composition varying subsystems (not shown in Figure 8A), as described above. The distribution manifold 500 is thermally isolated from the microreactors 600 by temperature control block 400. After contacting the candidate materials (*e.g.*, catalysts) 920 under reaction conditions, reactor effluent 60 is passed through connection channels 550 to a discharge manifold 501, and further to an external distribution (waste) system. The discharge manifold 501 can comprise a second set of outlet flow restrictors (not shown in Figure 8A). The discharge manifold 501 is likewise thermally insulated from the microreactors 600 by another temperature control block 400. Evaluation of the candidate materials can be determined by analysis of reaction products, for example, by sampling of the reactor effluent stream using one or more sampling probes 910 (*e.g.*, sampling needles) that are in selective fluid communication with one or more of the microreactors 600, and in further fluid communication with a detection system (*e.g.*, gas chromatograph, mass spectrometer, FTIR, *etc.*). A septum or other suitable accessible barrier 911 may be employed in connection with the sampling system. Reference is made to the earlier filed applications of Guan *et al.* (U.S. Patent No. 6,149,882) and especially Bergh *et al.* (U.S. Serial No. 09/518,794 now U.S. Patent No. 6,749,814) in connection with the embodiment shown in Figure 8A. A similar reaction system 10 is shown in Figure 8D, except that the outlet stream includes a “U-turn” to direct the effluent stream 60 to a discharge manifold 501 located in the vicinity of the inlet distribution manifold 500. This design has some advantages with

respect to flow control interfacing (localized area) and with respect to temperature control (single “cold zone”).

**\*\* Replace paragraph [0137] with the following replacement paragraph:**

**[0137]** An array of valves, preferably an array of microvalves can be employed in connection with the chemical processing systems of the invention (*e.g.*, a chemical reaction system 10 such as that shown and discussed in connection with Figure 8A), as well as with other chemical processing systems, such as those disclosed and discussed in the earlier-filed Bergh *et al.* application (U.S. Serial No. 09/518,794 now U.S. Patent No. 6,749,814). With reference to Figure 9A, for example, a pneumatically active microvalve array 2500 can comprise a plurality, and preferably four or more microvalves (2510 – not shown schematically) in operational communication with four or more microvalve actuators 2515 arranged and/or formed at, on or in a common substrate. The microvalve actuators can actuate the microvalves. In some embodiments, the common substrate can comprise a plurality of laminae, and the four or more microvalves and four or more microvalve actuators 2515 can be formed in the plurality of laminae. Each of the four or more microvalve actuators 2515 can be in selective fluid communication between a first pneumatic valve actuating line 2530a, 2530b of a first set 2530 of actuating lines, and a second pneumatic valve actuating line sample line 2550a, 2550b of a second set 2550 of actuating lines. Collectively, the four or more microvalve actuators are in selective fluid communication between the sets of first and second valve actuating lines 2530 and lines 2550. As shown, each of the four or more actuating flowpaths comprises an actuator inlet 2512 in fluid communication with at least one of the first actuating lines 2530a, 2530b, and an actuator outlet 2514 in fluid communication with at least one of the second actuating lines 2550a, 2550b, and in selective fluid communication with the actuator inlet 2512. A valve control logic 2514 can provide for selective, controlled actuation of the microvalve actuator 2515 for operation of valve 2510. One or more flow restrictors 2516 can be provided in the actuator flowpath (*i.e.*, between the actuator inlet 2512 and actuator outlet 2514), including for example as shown, between the microvalve actuator 2515 and the actuator outlet 2414. With reference to Figure 9B, the valve control logic 2514 can vary depending on the particular application, but can typically be an “AND” or an “OR” logic, such that valve control for four or more valves can be controlled using microprocessor based technology with appropriate software. Although shown

only with four or more microvalve actuators in the array, the number of microvalve actuators and microvalves can be substantially larger, including numbers that are the same as the number of reactors as described, for example, in the Guan *et al.* (U.S. Patent No. 6,149,882) and/or the Bergh *et al.* (U.S. Serial No. 09/518,794 now U.S. Patent No. 6,749,814) applications. As applied to chemical processing systems having arrays of larger numbers of components (*e.g.*, reactors; microvalve actuators) – such as 100 or more components, the number of actuation circuits can be increased by  $\log N$  (where  $N$  is the number of components) rather than being increased by  $N$  – which is the case with a hierarchy of individually-dedicated actuators. The array of microvalve actuators and microvalves can be fabricated by methods known in the art. *See*, for example: Rich *et al.*, “An 8-Bit Microflow Controller Using Pneumatically-Actuated Valves”, pp. 130-134, IEEE (1999); Wang *et al.*, “A Parylene Micro Check Valve”, pp. 177-182, IEEE (1999); Xdeblick *et al.*, “Thermopneumatically Actuated Microvalves and Integrated Electro-Fluidic Circuits”, 251-255, TRF, Solid State Sensor and Actuator Workshop, Hilton Head, South Carolina, June 13-16 (1994); and Grosjean *et al.*, “A Practical Thermopneumatic Valve”, 147-152, IEEE (1999). In operation, the array of microvalves and microvalve actuators can provide for selective sampling and multiplexing of a plurality and preferably four or more reactor effluent streams, and can be interfaced, for example, with detection instruments such as parallel GC and/or parallel MS, among others. Individual reactor effluent streams, or groups or subgroups of reactor effluent streams can be selectively sampled. The array of microvalves 2500 can be integrated with flow distribution systems, such as those disclosed herein, as well as with those disclosed in the Guan *et al.* and the Bergh *et al.*, and can be used with numerous other applications.

\*\* Replace paragraph [0145] with the following replacement paragraph:

**[0145]** The flow restrictor block 4510 includes six sets of flow-restrictor-groups microfabricated on separate microchip bodies 3650 that are mounted on a common substrate 3600. In one embodiment, a set of seven microchip bodies having integral flow restrictors can be mounted on a substrate, with each the flow restrictors in each of the ~~microchip~~~~microchip~~ bodies corresponding to one of the sets of flow-restrictor groups (SET A, SET B, SET C, SET D, SET E, SET F, SET CR) represented in Fig. 11B. Exemplary microchip bodies, corresponding to SET A and SET CR are shown in Figure 11D and 11E, respectively. The microchip bodies comprise a

first inlets 5002 (*e.g.* in fluid communication with one of the feed-component source gasses, such as the variable-feed component), and a second inlet 5004 (*e.g.*, in fluid communication with another of the feed-component source gas, such as the make-up feed component). When a particular set of flow restrictors is selected by actuation of microvalves (487, 489, Fig. 11B) corresponding to that set, then the two feed components come in through the inlets 5002, 5004 into the inlet plenums 5003, 5005, and flow through the flow restrictors (*e.g.*, for SET A, varied flow restrictors C1, C2, C4, C6, C8, C9; for SET CR, constant restrictors CR) to mixing zones 540, such that the varied feed compositions having various ratios of feed components are formed in the mixing zones. Microfluidic outlets 5010 provide fluid ~~communication~~communication to the discharge (channels 4540, Fig. 11B). As an alternative to the particular embodiment shown in Figure 2D, geometry effects associated with variously-sized channels off of the common inlet plenums 5003, 5005 (*e.g.* entrance volume effects) can be minimized physically forming, for example, the C9 flow restrictor from nine multiple, identical copies of the C1 flow restrictor. With reference to Figure 11F, in a further embodiment, the flow resistances on each particular microchip body be substantially the same (*e.g.*, C4, as illustrated, for one microchip body, C6 for another microchip body, *etc.*). Also, each flow restrictor (*e.g.*, C4, as illustrated) can have its own, dedicated ~~microfluidic~~microfluidic inlet 5002 and inlet plenum 5003. Referring to Figure 11G, the sets of flow restrictors (with grouped resistance values as shown in Figure 11B) can be established where each of the microchip bodies are fabricated to be identical (*e.g.*, such as shown in Figure 11D) – without physically and integrally rotating the various combinations of flow resistances on the microchip body – by having microfluidic channels 4540 that cross the outlets 5010 of each flow restrictor (C1, C2, C4, *etc.*) in the various combinations, so that by selection of appropriate feed components to the inlets 5002, the desired sets of flow restrictors (*e.g.* SET A, SET B, SETC, *etc.*) can be achieved. Internal passages within the flow-restrictor block 4520 and/or cover block 4510, 4504 can be used for internal interconnections. Such internal passages can be supplemented by external interconnections that interface through side ports 4544. Alternatively, such side-ports could be manifolded and routed through a different face of the flow-restrictor block 4510. Fabrication of the flow restrictors integral with the microchip bodies can be effected, for any of the aforementioned embodiments, using typical microfabrication techniques. Example 1 describes the fabrication techniques for an exemplary set of flow restrictor microchannels integral with a substrate or with a microchip body.

**\*\* Replace paragraph [0146] with the following replacement paragraph:**

**[0146]** The flow restrictor block 4510 also includes the six pairs of commonly-actuated inlet isolation microvalves 487, 489, as well as the outlet isolation valves 4580. These valves are preferably fabricated using precision machining techniques known in the art. Alternatively, the valves can be microfabricated, and can be integral with the flow-restrictor block 4510 or with a microchip body mounted thereon. The valves can also be, as noted above, part of an external fluid distribution system (480, Fig. 11b). The particular microvalve design is not critical. Preferably, the microvalves 487, 489 are membrane-actuated, membrane-seated valves such as shown in Figures 11H and 11I. Briefly, membrane-actuated valves 4300 can be prepared by precision machining to form the various component parts. In its open state (Fig. 11H), a fluid can flow into the valve through fluid inlet passage 4302, through internal passages 4303, past the valve seat 4310, and out through outlet passage 4304. In its closed state (Fig. 11I), a piston 4320 having a piston face 4322 is forced upward against a seating membrane 4315 such that fluid flow past the seat 4310 is sealingly blocked, with the seating membrane 4315 essentially acting as a gasket between the piston face 4322 and the valve seat 4310. The piston 4320 is preferably pneumatically actuated by use of an actuating membrane 4325 under pressure through actuation passage 4330. Portions of the seating membrane 4315 and actuating membrane that are situated between facing component surfaces of the valve body can serve as gaskets when the valve is clamped or fastened together. Further details are provided in co-pending, co-owned application U.S. Serial No. 60/274,022, entitled "Gas Chromatograph Injection Valve Having Microvalve Array" filed on the date even herewith (March 7, 2001) by Bergh *et al.* now perfected as U.S. Serial No. 10/092,364 filed March 6, 2002 by Bergh *et al.*, and as U.S. Serial No. 10/092,035 filed March 6, 2002 by Bergh *et al.*, now issued as U.S. Patent No. 6,742,544.

**\*\* Replace paragraph [0148] with the following replacement paragraph:**

**[0148]** The reactor module 4600, shown schematically in Figure 11O, comprises a 4x6 array of twenty-four reactor tubes 4610 individually supported in a reactor frame 4605. Each tube has a reaction volume of about 1 ml. Each of the reactor tubes 4610 can be individually heated using resistive coil heaters 4620 (*e.g.* Watlow Mini-K-ring). Thermal isolation between reactor tubes 4610 is achieved using fluid-type heat exchanger to cool the inter-reactor volume within the

reactor frame 4610. Preferably, the cooling medium is air or inert gas, and is fed into the reactor module 4600 substantially at the midsection thereof. Plate cooling fluid (*e.g.* air) is also fed through the top member 4606 and bottom member 4607 of the reactor frame 4605, specifically through heat-exchange channels 4608 formed therein. Advantageously, as described in greater detail above, the heat flux associated with the resistive coil heaters 4620 can be axially varied to account for heat variations due to the reaction, and to balance heat removal by the cooling media such that a substantially axial uniform temperature profile is obtained. Further details about temperature control are provided in co-owned, co-pending application U.S. Serial No. 60/274,065, entitled "Parallel Flow Reactor Having Improved Thermal Control" filed on the date even herewith (March 7, 2001) by Bergh *et al.* now perfected as U.S. Serial No. 10/094,257 filed March 7, 2002 by Bergh *et al.* The feed gas flows into the reactor tube inlet 4612, and optionally contacts a catalyst (*e.g.*, supported in the reactor tube using frits (not shown)) under reaction conditions to effect the chemical reaction of interest. The reaction products and unreacted reactants are discharged through the reactor tube outlet 4614.